PRACTICE POINTER

Metformin, heart failure, and lactic acidosis: is metformin absolutely contraindicated?

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Many patients with type 2 diabetes are denied treatment with metformin because of "contraindications" such as cardiac failure, which may not be absolute contraindications

Metformin first became available in the United Kingdom in 1957 but was first prescribed in the United States only in 1995.[w1] The mechanism of action has been extensively reviewed.[w2 w3] The UK prospective diabetes study showed that metformin was associated with a lower mortality from cardiovascular disease than sulphonylureas or insulin in obese patients with type 2 diabetes mellitus.[1] It was also associated with reduced all cause mortality, which was not seen in patients with equally well controlled blood glucose treated with sulphonylureas or insulin.[1]

Despite the evidence base for the benefits of metformin, concerns remain about its side effects and especially the perceived risk of lactic acidosis in the presence of renal, hepatic, respiratory, or cardiac failure.[2 w4 w5] Perhaps as a result of this, many suitable patients with type 2 diabetes are denied metformin treatment.[3 w6 w7] The box summarises the current contraindications to metformin use. In this article we review the evidence for the use of metformin in the presence of stated contraindications and especially for patients with heart failure.

Current contraindications to metformin use

Contraindications
- Renal dysfunction
- Congestive cardiac failure needing drug treatment
- Hypersensitivity to metformin
- Acute or chronic metabolic acidosis
- Impaired hepatic function

Precautions
- Age >80 years until renal dysfunction ruled out
- Acute myocardial infarction
- Radiological studies involving iodinated contrast
- Surgical procedures
- Alcohol intake

These contraindications/precautions have been increasingly challenged by recent evidence, although this evidence is mostly from observational studies

Table 1 | Summary of pharmacological differences between metformin and phenformin

Property	Metformin	Phenformin
Adherence to mitochondrial membrane[w2 w3]	Poor	Strong
Inhibition of electron transport chain[w2 w3]	Absent	Present
Inhibition of glucose oxidation[w3]	Absent	Present
Interference with lactate turnover[w3]	Absent	Present
Metabolism[w3]	Not metabolised/ excreted unchanged	Inactive hydroxylated derivative

These differences might explain the lower incidence of lactic acidosis with metformin.

Data sources

We searched Medline with the following terms: metformin, phenformin, biguanides, biguanide, lactic acidosis, lactic acid, heart failure, cardiac failure, congestive cardiac failure, left ventricular impairment, metformin contraindications, renal impairment, renal failure, diabetes, type 2 diabetes, non-insulin dependent diabetes, and combinations of these terms. In addition, we consulted the Cochrane systematic reviews.

Metformin and risk of lactic acidosis: what evidence?

The perceived risk of developing lactic acidosis with metformin is high, particularly in the United States. An increasing body of evidence challenges the so called "contraindications" to metformin.[4 5 w4 w7-w9] Most of the evidence for the association between metformin and lactic acidosis is historical data for phenformin (withdrawn in 1977).[6 w7 w8] Metformin is less likely than phenformin to cause lactic acidosis. Phenformin related lactic acidosis had an estimated incidence of 0.25-1 case per 1000 patient years compared with an estimated incidence of 0-0.09 case per 1000 patient years with metformin.[3 6 w3 w6 w10-w12] This difference in the incidence of lactic acidosis between metformin and phenformin could be due to more

stringent contraindications applied after the experience with phenformin. However, despite increased disregard of contraindications to metformin, as discussed below, the incidence of lactic acidosis has not increased.

Metformin and phenformin have different pharmacological characteristics that could explain the much lower incidence of lactic acidosis associated with metformin. Table 1 summarises some of these differences.

Evidence from case reports

Most case reports of lactic acidosis in people taking metformin have failed to provide adequate information to permit assessment of causation, including lactic acid concentrations and pH.[7] In a review of published case reports, Stades et al showed that plasma concentrations of metformin were not related to increased lactic acid concentration.[7] In addition, increased concentrations of neither lactic acid nor metformin were associated with increased mortality risk.[7] In contrast, acute cardiovascular events, liver cirrhosis, and sepsis were all associated with an increased mortality risk.[7] Interestingly, all but one of the cases in this review had at least one risk factor (renal failure, cardiovascular events, pulmonary failure, hepatic failure, alcohol excess, or sepsis) for the development of lactic acidosis independent of metformin use. Most of the patients developed lactic acidosis in the presence of acute or worsening renal failure. Creatinine concentrations, however, did not correlate with lactic acid concentrations, metformin concentrations, or mortality.[7]

Similar results were described by Lalau et al, who showed that neither lactate nor metformin concentrations were prognostically related to mortality and that death seemed to be related to other hypoxic disease or underlying ill health.[8] The median lactate concentrations were similar in patients who survived and those who died.[8] In addition, the median plasma metformin concentration was three times higher in patients who survived, which suggests that accumulation of metformin may not be as important in lactic acidosis as has been thought.[8] The lack of a relation between lactic acid/metformin concentrations and mortality and the absence of an association between metformin concentration and lactic acid concentration suggest that the association between lactic acidosis and metformin is coincidental,[7] although causality cannot be ruled out completely.

Epidemiological data

Brown et al collected 41 426 person years of data for patients with type 2 diabetes in the era before the introduction of metformin and found a rate of 0.097-0.169 events of lactic acidosis per 1000 person

Table 2 | **Summary of studies documenting non-adherence to standard contraindications/precautions to metformin and number of cases of lactic acidosis**

Study	No of patients taking metformin	Percentage with contraindications (≥1)	Contraindications	Lactic acidosis
Rakovac et al 2005[12]	4401	18.9	Alcohol consumption (250 g/week), renal impairment, and heart failure needing drug treatment	NA
Calabrese et al 2002[10]	204	44	Renal dysfunction (serum creatinine >133 µmol/l in men and >124 µmol/l in women), congestive heart failure needing drug treatment, acute or chronic metabolic acidosis, intravascular iodinated contrast material, age >80 years (unless measurement of creatinine clearance shows that renal function is not reduced), hepatic disease, concomitant cationic drug use, presence of any condition associated with hypoxaemia (such as chronic obstructive pulmonary disease and acute myocardial infarction), dehydration, sepsis, excessive alcohol intake, and after any surgery until patient's oral intake is resumed and renal function is deemed normal	0
Horlen et al 2002[11]	100	22	Documented heart failure, renal dysfunction (serum creatinine >132.6 µmol/l in men and >123 µmol/l in women)	0
Emslie-Smith et al 200[14]	1847	24.5	Acute myocardial infarction, cardiac failure, renal impairment, or chronic renal disease	1
Holstein et al 1999[6]	308	73	Renal impairment (creatinine clearance <60 ml/min), hepatic impairment, chronic respiratory failure, heart failure (ejection fraction <50%, lung congestion on radiograph), advanced coronary heart disease conditions, chronic alcohol misuse, severe infections, pregnancy/breast feeding, intravenous administration of contrast agents, and operations under general anaesthesia	0
Yap et al 1998[14]	70	94	Insulin dependent diabetes, hypersensitivity, impaired renal function, cardiovascular disease, conditions associated with hypoxia, serious liver dysfunction, excessive alcohol intake, concomitant use of diuretics, acute intercurrent illness, elderly, children, dehydration, serious infection, trauma, use of contrast	NA
Sulkin et al 1997[13]	89	54	Renal impairment, cardiac failure, chronic liver disease, ischaemic heart disease, clinical proteinuria, peripheral vascular disease, and pulmonary disease	0

NA=not available.

years.[9] This rate of lactic acidosis events is similar to that reported in patients with type 2 diabetes taking metformin,[9 w1 w11] which raises the possibility that the incidence of lactic acidosis in metformin treated patients might be related to type 2 diabetes rather than metformin treatment itself.[9] A Cochrane review of 206 comparative trials and cohort studies in patients with type 2 diabetes who were treated with metformin and had no contraindications to its use, found no evidence of increased risk of developing fatal or non-fatal lactic acidosis in the subgroup of metformin treated patients.[3] It also found no difference in lactate concentrations between patients treated with metformin or with non-biguanide drugs.[3]

Disregard of contraindications

Several reports found that physicians have increasingly ignored contraindications to prescribing metformin and yet the incidence of lactic acidosis has remained very low (table 2).[4 6 10-14 w7] Emslie-Smith et al, in a population based study in Scotland between January 1993 and June 1995, found that 24.5% of patients receiving metformin had contraindications to its use, including acute myocardial infarction, cardiac failure, renal impairment, or chronic renal disease. Despite this, only one episode of lactic acidosis occurred in 4600 patient years, and this was in a 72 year old patient with acute myocardial infarction complicated by acute renal failure.[4] A cross sectional analysis, by Holstein et al, of 308 consecutive type 2 diabetes patients treated with metformin from 1 January 1995 to 31 May 1998 found that 73% of these patients had at least one contraindication to the use of metformin.[6] None the less, no cases of lactic acidosis were seen.[6] Contraindications in the study by Holstein et al included renal impairment (creatinine clearance <60 ml/min), hepatic impairment, chronic respiratory failure, heart failure (ejection fraction <50%, lung congestion on radiograph), advanced coronary heart disease conditions, chronic alcohol misuse, severe infections, pregnancy or breast feeding, intravenous administration of contrast agents, and operations under general anaesthesia. Of note, none of the patients in the UK prospective diabetes study developed lactic acidosis.[1] The study protocol, however, would have ensured that metformin was not used in patients with contraindications.

Table 2 summarises the studies that have shown increased disregard of contraindications to metformin and the contraindications used in each study. However, these studies are observational, so confounding factors, particularly confounding by indication, affecting the outcome could not be excluded. In addition, the percentage of patients taking metformin who have at least one contraindication varies considerably. The evidence from these reports reinforces the viewpoint that metformin is an extremely rare cause of lactic acidosis in patients with type 2 diabetes, even in the presence of contraindications including renal, hepatic, and cardiac failure.

Cardiac failure and metformin

Patients with type 2 diabetes are at an increased risk of developing congestive cardiac failure compared with patients without diabetes.[15 w13] In one study by Nichols et al, the incidence of developing cardiac failure among patients with type 2 diabetes was 30.9 cases per 1000 person years compared with 12.4 cases per 1000 person years in patients without diabetes, a relative risk of 2.5.[15] The difference between the rates of cardiac failure was even greater among the younger age groups.[15] In the same study, age, ischaemic heart disease, poorer glycaemic control, and greater body mass index were predictors of the development of cardiac failure.[15] The UK prospective diabetes study estimated the incidence of cardiac failure in patients with type 2 diabetes to be 2.3-11.9 per 1000 person years.[16] Diabetes is also an independent predictor of mortality in patients admitted to hospital with cardiac failure.[17 w13] This risk is particularly high in women.[17]

Cardiac failure is usually considered to be a contraindication to metformin treatment and is withheld from large numbers of patients with type 2 diabetes and coexistent cardiac failure. More recent studies suggest that metformin may not be absolutely contraindicated and could be beneficial in such patients.[5 18 19] It improves glycaemic control and has a favourable effect on other cardiovascular risk factors, including lipids.[18 w3] The UK prospective diabetes study has shown that it reduces mortality and macrovascular end points in patients with type 2 diabetes, although these patients did not have heart failure.[1]

Table 3 | Adjusted odds ratios (95% confidence intervals) from an observational population study by Johnson et al and adjusted hazard ratios (95% confidence intervals) from observational studies in patients with cardiac failure by Eurich et al and Masoudi et al

	All cause mortality			All cause hospital admissions			Cardiovascular disease deaths		
Study	Metformin	Sulphonylurea	Metformin plus sulphonylurea	Metformin	Sulphonylurea	Metformin plus sulphonylurea	Metformin	Sulphonylurea	Metformin plus sulphonylurea
Johnson et al 2002[18]	0.60 (0.49 to 0.74)	1	0.66 (0.58 to 0.75)	NA	NA	NA	0.64 (0.49 to 0.84)	1	0.64 (0.54 to 0.77)
Eurich et al 2005[19]	0.70 (0.54 to 0.91)	1	0.61 (0.52 to 0.72)	0.87 (0.73 to 1.05)	1	0.93 (0.83 to 1.05)	NA	NA	NA
Masoudi et al 2005[5]	0.86 (0.78 to 0.97	0.99 (0.91 to 1.08)	NA	NA	NA	NA	NA	NA	NA

NA=not applicable.

Canadian population data

The Saskatchewan health database (in Canada) was used to examine population based mortality for new users of oral hypoglycaemic agents.[19] The researchers identified patients with prescriptions for sulphonylurea or metformin in 1991-6. They followed prescription records prospectively for between one and nine years; patients with any insulin use were excluded. The different groups were controlled for age, sex, comorbidity, and the presence of coronary artery disease. Data from 8866 patients (3033 sulphonylurea monotherapy, 1150 metformin monotherapy, and 4683 combination treatment) were reported. One hundred and fifty nine (13.8%) deaths occurred in the metformin monotherapy group and 635 (13.6%) in the combination treatment group, compared with 750 (24.7%) deaths in the sulphonylurea monotherapy group. The numbers of cardiovascular related deaths were 80 (7.0%) in the metformin monotherapy group, 299 (6.4%) in the combination group, and 351 (11.6%) in the sulphonylurea monotherapy group.

Table 3 summarises the results of this study, including the odds ratios and confidence intervals. Metformin, alone or in combination with sulphonylurea, was associated with reduced all cause and cardiovascular mortality compared with sulphonylurea monotherapy among new users of these agents. The main limitation of this study is that it is observational and based on an administrative database, so the data on drug prescription may not exactly reflect the drug consumption. The authors claim that their database is known for its quality.[19] In addition, because of the observational nature of the study, confounding factors such as confounding by indication cannot be ruled out.

Canadian cardiac failure data

In a more recent study using the same database, Eurich et al compared the clinical outcomes of patients with type 2 diabetes who were known to have cardiac failure and were on metformin alone, sulphonylurea alone, or combination treatment.[18] They identified 2793 patients with type 2 diabetes who were treated with oral hypoglycaemic agents and had a hospital admission with heart failure between 1991 and 1996. Patients who were on insulin or had had heart failure for more than three years before starting oral hypoglycaemic agents were excluded, and 1833 patients were eligible for the study. Patients were followed up for a period of between one and nine years, and the primary outcome was all cause mortality at one year (short term) and at the end of follow-up (long term). Secondary outcomes were all cause hospital admissions at one year and long term. The researchers also evaluated the effects of oral hypoglycaemic agents on composite outcomes, including all cause hospital admission and all cause mortality. At one year, compared with the 200 (26%) deaths in the sulphonylurea monotherapy group, 29 (14%) deaths occurred in the metformin monotherapy group (unadjusted hazard ration 0.52, 95% confidence interval 0.35 to 0.76) and 97 (11%) deaths (unadjusted hazard ratio 0.41, 0.32 to 0.52) in the metformin-sulphonylurea combination group. After controlling for age, sex, drugs known to affect outcomes of heart failure, and total physician visits before diagnosis of heart failure, the authors found that metformin alone (adjusted hazard ratio 0.66, 0.44 to 0.97) or in combination with other agents (0.54, 0.42 to 0.70) was associated with reduced one year all cause mortality compared with sulphonylurea monotherapy in patients with heart failure. The long term mortality and morbidity in patients treated with metformin, alone or in combination with other antidiabetic agents, was lower than that observed for patients treated with sulphonylurea only (52% for sulphonylurea monotherapy *v* 33% for metformin monotherapy *v* 31% for combination treatment).[18]

Table 3 summarises the long term outcomes of this study, including hazard ratios and 95% confidence intervals. The all cause hospitalisation was significantly lower in the metformin monotherapy group compared with sulphonylurea monotherapy or combination treatment both at one year and long term. Similar to the previous study by Johnson et al, one of the main limitations is that this study is observational and based on a database, which means that drug prescription may not reflect exposure and that confounding by indication could not be ruled out. Another important limitation is that the investigators did not have any information about the severity of heart failure and the presence or absence of renal failure. The latter is particularly important, as renal failure is an independent predictor of poor prognosis in heart failure. If the metformin group had less renal failure, this would affect the validity of the results. This is unlikely, however, as renal dysfunction is very common in patients with heart failure,[20] so a considerable proportion of patients in all groups are likely to have had renal impairment.

US cardiac failure data

Masoudi et al found similar results. They evaluated the impact of insulin sensitisers (metformin or thiazolidinediones) on outcomes in patients with type 2 diabetes and cardiac failure.[5] Crude one year mortality was lower among patients treated with a thiazolidinedione (30.1%) or metformin (24.7%) compared with patients treated without insulin sensitising drugs (36.0%; P=0.0001 for both comparisons).[5] Treatment with thiazolidinedione (hazard ratio 0.87, 0.80 to 0.94) or metformin (0.86, 0.78 to 0.97) was associated with significantly lower risks of death.[5] No significant association was found between treatment with sulphonylurea (0.99, 0.91 to 1.08) or insulin (0.96, 0.88 to 1.05) and mortality.[5] Admissions for all causes did not differ with either insulin sensitiser, although the risk of readmission for heart failure was higher in those receiving thiazolidinedione (1.06, 1.00 to 1.09) and lower with metformin treatment (0.92, 0.92 to 0.99).[5] The study was an observational retrospective cohort, so the results should be interpreted with caution. Although the authors made adjustments for a

SUMMARY POINTS

Treatment with metformin is not associated with an increased risk of lactic acidosis among patients with type 2 diabetes mellitus who have no cardiac, renal, or liver failure

Despite increasing disregard of contraindications to metformin by physicians, the incidence of lactic acidosis has not increased, so metformin may be safe even in patients with "contraindications"

The vast majority of case reports relating metformin to lactic acidosis report at least one other disease/illness that could result in lactic acidosis

Use of metformin in patients with heart failure might be associated with lower mortality and morbidity, with no increase in hospital admissions and no documented increased risk of lactic acidosis

Further studies are needed to assess the risk of lactic acidosis in patients with type 2 diabetes and traditional contraindications to metformin

wide range of variables, including markers of severity of heart failure and comorbidities, variations in the institution and clinician who treated the patients may influence the results. Consequently, these results could reflect the influences of unmeasured confounding factors, including confounding by indication.

Conclusions

An increasing body of evidence suggests that metformin treatment alone will not result in lactic acidosis unless other contributing factors coexist. More importantly, treatment with metformin is not absolutely contraindicated in patients who have isolated heart failure, and it may be beneficial. The risk of lactic acidosis due to metformin is negligible in these patients and is unrelated to the plasma concentration of metformin. The presence of other organ failure, such as renal failure, in addition to heart failure might still pose a risk of lactic acidosis. Metformin provides a greater degree of cardiovascular protection than would be expected from its antihyperglycaemic actions alone and is the first drug of choice for the treatment of type 2 diabetes.[w14] The decision to stop or continue metformin in the presence of heart failure should be individualised to the particular patient until further evidence is available.

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1 UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998;352:854-65.
2 Glucophage. www.fda.gov/medwatch/SAFETY/2004/mar_PI/Glucophage_PI.pdf (accessed 6 July 2007).
3 Salpeter S, Greyber E, Pasternak G, Salpeter E. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2006;(1):CD002967.
4 Emslie-Smith AM, Boyle DI, Evans JM, Sullivan F, Morris AD. Contraindications to metformin therapy in patients with type 2 diabetes—a population-based study of adherence to prescribing guidelines. *Diabet Med* 2001;18:483-8.
5 Masoudi FA, Inzucchi SE, Wang Y, Havranek EP, Foody JM, Krumholz HM. Thiazolidinediones, metformin, and outcomes in older patients with diabetes and heart failure: an observational study. *Circulation* 2005;111:583-90.
6 Holstein A, Nahrwold D, Hinze S, Egberts EH. Contra-indications to metformin therapy are largely disregarded. *Diabet Med* 1999;16:692-6.
7 Stades AM, Heikens JT, Erkelens DW, Holleman F, Hoekstra JB. Metformin and lactic acidosis: cause or coincidence? A review of case reports. *J Intern Med* 2004;255:179-87.
8 Lalau JD, Race JM. Lactic acidosis in metformin-treated patients: prognostic value of arterial lactate levels and plasma metformin concentrations. *Drug Saf* 1999;20:377-84.
9 Brown JB, Pedula K, Barzilay J, Herson MK, Latare P. Lactic acidosis rates in type 2 diabetes. *Diabetes Care* 1998;21:1659-63.
10 Calabrese AT, Coley KC, DaPos SV, Swanson D, Rao RH. Evaluation of prescribing practices: risk of lactic acidosis with metformin therapy. *Arch Intern Med* 2002;162:434-7.
11 Horlen C, Malone R, Bryant B, Dennis B, Carey T, Pignone M, et al. Frequency of inappropriate metformin prescriptions. *JAMA* 2002;287:2504-5.
12 Rakovac I, Jeitler K, Gfrerer RJ, Habacher W, Seereiner S, Mrak P, et al. Patients with type 2 diabetes treated with metformin: prevalence of contraindications and their correlation with discontinuation. *Diabet Med* 2005;22:662-4.
13 Sulkin TV, Bosman D, Krentz AJ. Contraindications to metformin therapy in patients with NIDDM. *Diabetes Care* 1997;20:925-8.
14 Yap WS, Peterson GM, Vial JH, Randall CT, Greenaway TM. Review of management of type 2 diabetes mellitus. *J Clin Pharm Ther* 1998;23:457-65.
15 Nichols GA, Gullion CM, Koro CE, Ephross SA, Brown JB. The incidence of congestive heart failure in type 2 diabetes: an update. *Diabetes Care* 2004;27:1879-84.
16 Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000;321:405-12.
17 Gustafsson I, Brendorp B, Seibaek M, Burchardt H, Hildebrandt P, Kober L, et al. Influence of diabetes and diabetes-gender interaction on the risk of death in patients hospitalized with congestive heart failure. *J Am Coll Cardiol* 2004;43:771-7.
18 Eurich DT, Majumdar SR, McAlister FA, Tsuyuki RT, Johnson JA. Improved clinical outcomes associated with metformin in patients with diabetes and heart failure. *Diabetes Care* 2005;28:2345-51.
19 Johnson JA, Majumdar SR, Simpson SH, Toth EL. Decreased mortality associated with the use of metformin compared with sulfonylurea monotherapy in type 2 diabetes. *Diabetes Care* 2002;25:2244-8.
20 McAlister FA, Ezekowitz J, Tonelli M, Armstrong PW. Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study. *Circulation* 2004;109:1004-9.

Endpiece

Evil in the United States in 1834

Eating too much, and of unwholesome articles, is a national evil in the United States; and were I to add, a national disgrace, the charge would not be too severe… It is much easier to procure the means of indulging to excess, in the United States, than in any other country… mankind are prone to the gratification of the palate, and other animal appetites, in proportion to the facilities of indulgence they enjoy. I confidently believe, that the thirteen or fourteen millions of people, inhabiting this country, eat more rash, for amusement, and fashion's sake, and to pass away idle time, than half the inhabitants of Europe united. Unquestionably they consume a greater amount of such articles, in the proportion of five to one, than an equal number of the people of any other country I have ever visited.

Caldwell C. *Thoughts on physical education.* Boston: Marsh, Capen and Lyon, 1834: 51-2

Submitted by Jeremy Hugh Baron, honorary professorial lecturer, Mount Sinai School of Medicine, New York